REMARKS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RE:	Patent Application for Bullock	Date:	December 16, 2005
Serial No.:	09/886,937	Art Unit:	1638
Filed:	6/21/2001	Examiner:	Helmer, Georgia
For:	Shaken Not Stirred	Action:	Response to Office Action

To: The Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

REMARKS

This is in response to the Office Action dated September 9, 2005. A one month extension of time in duplicate is enclosed.

Claims Rejections- 35 USC §112

Claims 1-5 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner has indicated that the claim language "for less than 10 seconds" is not supported by the originally filed specification or claims. The Applicant's attorney has removed this language from the claim and replaces it with "5-20 seconds". However, the Applicant's attorney would like to note that a method of shaking of "less than 10 seconds" is shown on pages 32, 33 and 36 where the time frames were 20, 10 and 5 seconds of shaking.

Claims Rejection – 35 USC §102(b)

The Examiner has rejected claims 1, 4 and 5 as being anticipated by *Coffee*, et al., US 5,302,523 in combination with secondary reference (coleparmor.com catalog page). Anticipation has been addressed by the Federal Circuit. According to *Helifix Ltd. V Blok-Lok, Ltd.,* 208 F.2d 1339, 54 USPQ2d 1299 (Fed. Cir. 2000), an invention is anticipated under 35 U.S.C. § 102(b) if it "was . . .

described in a printed publication in this . . . country . . . more than one year prior to the date of application for patent in the United States." 35 U.S.C. § 102(b). Analysis of anticipation is a two step process. The first step of an anticipation analysis is claim construction. See, Key Pharms. v. Hercon Labs. Corp., 161 F.3d 709, 714, 48 USPQ2d 1911, 1915 (Fed. Cir. 1998). The second step in an anticipation analysis involves a comparison of the construed claim to the prior art. See Key Pharms., 161 F.3d at 714, 48 USPQ2d at 1915. To be anticipating, a prior art reference must disclose "each and every limitation of the claimed invention[,] . . . must be enabling[,] and [must] describe . . . [the] claimed invention sufficiently to have placed it in possession of a person of ordinarily skill in the field of the invention." In re Paulsen, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994).

The first step requires us to look at claim one as amended:

1. (currently amended) An improved method of introducing ~~a~~ at least one nucleic acid into at least one plant ~~cells~~ cell comprising the steps of: providing a whisker cocktail comprising (i) at least one cell, (ii) a multiplicity of whiskers and (iii) at least one nucleic acid, and the improvement comprising employing a device for shaking ~~for less than 10 seconds~~ said whisker cocktail with a shaking motion of less than 2100 cycles per minute and more than 350 cycles per minute, for 5-20 seconds, so as to create collisions between said whiskers and said plant cells whereby at least one of said nucleic acid is introduced into at least one of said plant cells.

Claim 1 requires an improvement of employing a device for shaking the cocktail with a shaking motion of less than 2100 cycles per minute and more than 350 cycles per minute.

Claims 4 and 5 further narrow the parameters of the number of cycles per minute. Claim 4 lowers the cycles to less than 1000. Claim 5 lowers the cycles to a range around 760.

The next step in an anticipation analysis is a comparison of the construed claim to the prior art. The examiner cited the following prior art in the §102 (b) rejection - U.S. patent 5,302,523 ('523) to *Coffee*, and the Examiner cited a 2005 Cole-Parmer Instrument Company catalog page listing Genie® (a trademark of Cole-Parmer Instruments Company) vortexing devices to evidence the state of the art of vortexing machines.

The applicant's attorney has already indicated that the U.S. Patent '523 should not be combined with the 2005 catalog to make a 102 rejection. According to *Nystrom v. Trex Co.*, 374 F.3d 1105, 1 USPQ2d 1241 (Fed. Cir. 2004), "A patent is invalid as anticipated if every limitation in a claim is found in a single prior art reference." In other words, "Anticipation under 35 U.S.C. § 102 requires that a single prior art reference disclose each and every limitation of the claimed invention." Electro Med. Sys. S.A. v. Cooper Life Sci., 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994), as cited by Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 66 USPQ2d 1429 (Fed. Cir. 2003), the '523 patent does not fulfill this requirement. The time limit of claim 1 is not shown, nor is the range of cycles shown in '523.

The question becomes what does the U.S. patent '523 teach. This patent suggests in its description, without providing an example or instructions that,

> In one embodiment of the invention a quantity of the needle-like bodies is added to a liquid suspension of the cells to be transformed and the mixture agitated, **for example by stirring**, so that the moving cells and bodies interact resulting in penetration of the cell wall of the cells.

One method comprises mixing the DNA and fiber suspension, then adding this mixture to the cell suspension. **The final mixture is vortexed together.** The cells can then be incubated, and tested for expression of recombinant DNA.

In fundamental principle, this type of transformation utilises a procedure which penetrates the cell wall in a non-lethal manner. Such methods, then, seek to wound but not kill the cells. **In investigating possible procedures, it may be assumed that if particular method is capable of killing the cells then by making the treatment less severe the method may be adapted to wound.**

This patent teaches the following in example one:

Initial experiments were performed using LO56 cells in a total volume of 1.75 ml of cell suspension, whiskers and medium (1.0 ml cell suspension, 3 days post culture; 0.5 ml sterile distilled water, to reduce osmolality and 0.25 ml of whisker suspension) using two vortex durations, 90 and 180 seconds. **Vortexing was conducted using a standard Gallenkamp (Trade Mark) laboratory vortex mixer in either 10 or 50 ml sterile plastic centrifuge tubes.**

The patent teaches the following in example two:

Transformation was carried out as follows: 75 .mu.g of plasmid DNA was vortexed for 10 seconds with 80 .mu.l of the fibre suspension. A cell suspension, consisting of 250 .mu.l of packed 3 day-old BMS cells resuspended in 100 .mu.l sterile water with an osmolarity of 125 mOsM/kg, was then added to the DNA/fibre suspension. **This mixture was vortexed together for 60 seconds using a standard desktop vortex mixer at the highest possible speed. The**

conditions used were those found to be optimal for transforming BMS cells.

An "anticipating" reference must describe all of the elements and limitations of the claim in a single reference, and enable one of skill in the field of the invention to make and use the claimed invention. Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1378-79 (Fed. Cir. 2001); Richardson v. Suzuki Motor Co., 868 F.2d 1226 (Fed. Cir. 1989). The *Coffee* patent does not teach nor suggest the shaking motion of less than 2100 cycles per minute and more than 350 cycles per minute. *Coffee* also does not teach or suggest less than 1000 cycles or a range around 768 cycles, nor the length of time.

The combination of the Genie vortexer 2005 catalog with the patent is not appropriate in a §102 rejection. The Examiner alleges that the reference is applied to both explain the meaning of a term used in the primary reference and show that a characteristic not disclosed in the reference is inherent. The Applicant's attorney notes that even if the Examiner is using the reference for one or both of these reasons, it is still inappropriate because the ultimate reason is to attempt to supply a missing claim limitation, which is inappropriate.

Application of the rule of law in the court's holdings on the use of additional references in Studiegesellschaft disqualifies this catalog reference as an additive reference because the reference is an attempt to supply a missing claim limitation. Studiegesellschaft states, "Although we have permitted the use of additional references to confirm the contents of the allegedly anticipating reference", see id., "We have made clear that anticipation does not permit an additional reference to supply a missing claim limitation." See Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc., 726 F.2d 724, 727, 220 USPQ 841, 842 (Fed. Cir. 1984).This catalog is an unpermitted additional reference to the *Coffee* patent and the combination is not an appropriate §102 rejection.

The Examiner has indicated that the information from the 2005 catalog page on Genie vortexing machines evidences of what vortexing mixers were like at the time of filing and thus the catalog is appropriate as an additional reference under the §102 rejection. The Applicant respectfully disagrees that this catalog can be used in this manner as an additional reference.

However, the applicant is not indicating and is not trying to indicate that at the time of filing this application vortex mixing was not known. In fact, vortexing with the whiskers technology had been taught by *Coffee*. What the applicant is claiming is that the use of the claimed invention was not taught nor was it suggested nor was it obvious at the time of filing this application.

This combination of the two references is not appropriate for two distinct reasons: 1) the only vortex device specifically discussed is not the Genie but the 'Gallenkamp', and 2) the catalog provides that the Genie has a range of rpms, however, the patent indicates that the optional parameters are the highest possible speed of the vortex machine, which is not a range of speeds.

Turning to reason 1, according to the patent, "**Vortexing was conducted using a standard Gallenkamp (Trade Mark) laboratory vortex mixer",** therefore the Genie vortexing device was not the device employed in the invention, therefore the additive catalog is not further defining what the patent taught.

Moving on to reason two, according to the patent, "This mixture was vortexed together for 60 seconds using a **standard desktop vortex mixer** *at the highest possible speed.*" If this clause is read to include vortex mixers generally, even in that instance, the Genie vortex device in the catalog in association with the patent still does not teach the present claimed invention. The general vortex mixer mentioned in the specification, is described as being used for vortexing at the highest possible speed. The highest possible speed of the Genie vortexer as

shown in the 2005 catalog is 2700 rpm. There is no indication in the patent specification or in the catalog information that the range of less than 2100 cycles per minute and more than 350 cycles per minute as claimed in claim1 should or even could be employed. The parameters in claims 4 and 5 are also not shown. The only teaching in the specification is to vortex **using a standard desktop vortex mixer at the highest possible speed.** The specification then notes that the, "**conditions** used were those found to be **optimal** for transforming BMS cells."

(bold added for emphasis by applicant's attorney)

Therefore, if we apply the rule of law of *Teleflex, Inc. v Ficosa North American Corp.*, 299 F.2d 1313, 63 USPQ2d 1374 (Fed. Cir. 2002) as we have repeatedly stated, anticipation requires that each limitation of a claim must be found in a single reference. See, e.g., In re Donohue, 766 F.2d 531, 534, 226 USPQ 619, 621 (Fed. Cir. 1985). And the court's holdings on the use of additionally references in Studiegesellschaft states that, "Although we have permitted the use of additional references to confirm the contents of the allegedly anticipating reference, see id., we have made clear that anticipation does not permit an additional reference to supply a missing claim limitation." See Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc., 726 F.2d 724, 727, 220 USPQ 841, 842 (Fed. Cir. 1984). We are lead by the facts and the caselaw to the irrefutable conclusion that the catalog is an unpermitted additional reference, because it is an attempt to supply a missing claim limitation.

Even if the additive reference of the catalog was appropriate, then the catalog, read in light of the *Coffee* patent, still does not amount to a 102(b) anticipating set of references, because there is no teaching in either reference of the specific range of cycles in the claim.

The Examiner indicated that the Applicant had not provided evidence that the paint shaker of claim 6 and the parameters of the other method claims were not an obvious variant of the vortex machine. It is difficult to understand how claim 6,

which specifically claims the use of a paint mixer, could be considered an obvious variant of either a vortex mixer as taught by *Coffee* or a Mixomat as taught in WO 94/28148 to Bagnall.

A paint shaker machine is not standard equipment in a biology lab. A paint shaker machine is used to interdisperse a liquid pigment within a liquid paint. A paint shaker is not designed to hold or handle biological material and it is not designed nor is there any suggestion that it should be used to agitate in a transformation process.

In determining what was an obvious variant the Office must look at the ordinarily skilled person in the art. The ordinarily skilled person is most likely a Master or PhD level molecular biologist. The problem encountered in the art is introducing DNA by transformation methods while avoiding cellular inviability. The use of a whiskering transformation method was addressed in WO 94/28148 to Bagnall. This application used an office instrument called a Mixomat. This device like the vortexing device is a scientific instrument adapted for mixing of material in test tubes and small vials. WO 94/28148 to Bagnall teaches that the Mixomat device used (which was only used for 1 second, see Table 11, page 25) even for a very short duration resulted in less viability of the cell, than use of the vortex mixer. See page 23 (entire page), but also note line 32 where even 5 seconds of Mixomat treatment caused reduction in the number of stably transformed lines. The solutions to the prior art problems taught in the Bagnall reference was to consider the cell survival see page 25 line 15. This solution would not lead the ordinarily skilled person to employ a very vigorous shaking device such as the paint shaker. The ordinarily skilled person would not see a violent paint shaking machine found not in the lab but instead in a hardware store as the likely solution to the problem of introducing DNA into cells. In fact, in light of the teaching of WO 94/28148 to *Bagnall*, the ordinarily skilled person would have been much more prone to solve the problem with a gentle vortexing with a lab machine than

employing a violent shaking by a machine which was not adapted for biological material.

The invention taught in claim 1 is also not an obvious variant of the methods of whiskering previously taught. In claim 1, it is clear that what is being employed is a shaking action. This is a defined term that differs from the mixing and vortexing action. The shaking action and the paint mixer are not obvious variants of the vortex mixer nor of the Mixomat.

The shaking action is really taught away from by both *Coffee* and *Bagnell*. This is because the *Coffee* indicates that it taught optimal parameters for vortexing and these were 60 seconds at the highest speed of a vortex mixer. There is no suggestion that a shaking motion could be employed. The teaching of *Bagnell* is that the Mixomat even at five seconds of use was causing cell death and not particularly helpful in whiskering cells.

Again going to the ordinarily skilled person the courts have indicated the following:

> {Instead,} The court should have considered the educational level of the inventor; the type of problems encountered in the art; the prior art solutions to those problems; the rapidity with which innovations are made; the sophistication of the technology, and the educational level of workers in the field. See Custom Accessories, 807 F.2d at 962, 1 USPQ2d at 1201.

The applicant would like to draw the Examiner's attention to the Genie Shaker article that the Examiner produced. Even though the Applicant believes that this article is not properly a part of prior art, the article does indicate exactly what the applicant's attorney has been saying. The applicant's attorney's position is that the shaker machine was not obvious. Shaking was not obvious because shaking was employed in biological labs to lyse cells. In the article supplied by

the Examiner the Disruptor Genie shaker is shown. This shaker has the same speed range as the other vortexing machines and the same power and overall dimensions. The only real difference that appears is in the description—it notes that this machine features dramatically increased disruption efficiency – ideal for difficult bacterial cell disruption/homogenization. The information also indicates that the multidirectional action simultaneously agitates and vortexes at high-speed.

In light of the fact that intense shaking were used and known to cause cell disruption and cell lyse the ordinarily skilled person in the art would not be led to use a paint shaker or the cycle range claimed in claim1 to try and introduce DNA with sharp pointed silicon whiskers into cells. This is particularly true because transformation of cells will not work if cells are lysed. The cell must be capable of survival or it is useless.

The primary objective of the invention as claimed herein is to get DNA into the cells with the use of whiskers and then to regenerate the cells containing the DNA. Selecting a technology which is known to lyse cells – which, of course, renders the cells unviable and therefore not useful for regeneration, would not be an obvious choice. In fact, the disruption and lysing of cells should have led the ordinarily skilled person in the art of transformation to look for gentler means of mixing the cells with the whiskers not a more intense means of mixing, such as shaking the cells.

The applicant's attorney has attached a review by the author, Tim Hopkins, of the book *Purification and Analysis of Recombinant Proteins,* Seetharam and Sharma, editors, published by Marcel Dekker, Inc., 1991. This review indicates that a practical way to mechanically cause cell disruption is through using bead milling, which is a "...large number of minute glass or ceramic beads are vigorously agitated by shaking or stirring. Disruption occurs by the crushing action of the glass beads as they collide with the cells. The method has been used for years to disrupt microorganisms and works successfully with tough-to-

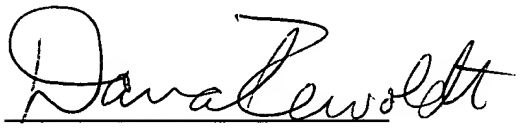
disrupt cells ... More recently, bead mill homogenization has been applied to soil samples and to plant and animal tissue."

Thus in 1991 when the book that was reviewed was written it was known and understood that placing 'minute' beads, which are rounded and vigorously shaking would cause cell disruption for the extraction of the nucleic acids, viruses, intracellular organelles and the like.

In contrast, the inventors of the present invention needed a shaking method that would allow the DNA to enter the cells without the cells being destroyed. The invention needed the cells to remain viable. It is counter intuitive to think that employing this type of method (shaking) with sharp pointed whiskers would produce viable cells. This is very true when the method employing rounded beads was known to produce disrupted pieces of the subcellular material from the once intact cell. It is even more difficult to understand why the inventors selected the method when the attached article notes that selective disruption can be obtained with larger beads or smaller charges of beads or shorter disruption times. The shaking method is never taught nor suggested by the references. The applicant's attorney has supplied additional references to show mechanical methods of lysing cells.

What the inventors needed were viable cells without any disruption of or destruction of the functions of the cells. There was no suggestion that vortexing or bead mills or mechanical cell disruption by vigorous shaking would accomplish this. The inventors needed a cell that had the DNA introduced in a manner that left the cell capable of being used for regeneration and the prevailing knowledge at the time indicated that use of a vigorous agitation by shaking or stirring with the presence of a rounded bead would accomplish the disruption and lysing of the cell, not the desired result a transformed cell.

The Examiner is requested to reconsider the rejections in light of the amendments and in light of the articles and arguments, and if appropriate remove the rejections to the claims.



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I hereby certify that the Response to Office Action dated September 9, 2005 is being mailed to the Commissioner for Patents, Alexandria, VA 22313-1450, on this16th day of December, 2005.